Review of Pre-licensure Safety Data and Update

LYMErix® Lyme Disease Vaccine

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Lyme Disease (LD) Background

- **LD first recognized in mid-late 1970s**
- **Most common U.S. vector-borne disease**
- **Endemic in several regions in U.S.**
- **>90% reported by about 150 counties in Northeastern & mid-Atlantic seaboard & upper North-central U. S.**
- **Peak disease transmission - late spring & summer - feeding of nymphal ticks, most common source of human infection**

Phase 3 Pivotal Efficacy Trial

- **Prospective, multi-center, RDBPCT**
- **Conducted over 2 disease transmission seasons**
- **31 study sites in areas endemic for LD**
- **10,936 healthy adults (15-70 years)**
- **5,469 received ≥ 1 dose Lyme disease vaccine**
- **5,467 received ≥ 1 dose placebo (adjuvant alone)**
- **Vaccination IM at 0, 1, 12 months**
- **Observation period = 20 months**

Exclusions - Efficacy Trial

- **Physician diagnosed chronic joint or neurologic illness related to LD**
- **Current disease associated with joint swelling or diffuse joint or muscular pain**
- **Known 2^{nd}/3^{rd} degree atrio-ventricular heart block or cardiac pacemaker**
- **Pregnancy or breastfeeding**

Demographics - Efficacy Trial

- 42% females, 58% males
- 98.3% white, 0.3% black, 0.1% Oriental, 1.3% other
- Treatment groups similar in terms of age & gender
- Mean age = 46 years (range 14-70 years)
- One protocol violation - aged 14 years

Efficacy Trial

- **Prevention of definite cases of LD**
  - **Year 1: 50% (95% CI: 14 to 71%)**
  - **Year 2: 78% (95% CI: 59 to 88%)**
- **No differences in LD manifestations in vaccinees vs. placebo recipients**

Lyme Disease Manifestations Occurring During Efficacy Trial

- 128 reports of erythema migrans
  - (32 vaccine, 96 placebo)
- 1 report of arthritis (vaccine)
- 1 report of trigeminal neuralgia (placebo)
- 1 report of facial palsy (placebo)
- Of 128 subjects presenting w/ erythema migrans
  - 3 reported facial palsy (1 vaccine, 2 placebo)
  - 1 reported trigeminal neuralgia (placebo)

Safety Monitoring Efficacy Trial

- **“Solicited” adverse events - 938 subjects**
  - **4 day diary cards w/ specific queries**
- **Routine monitoring of all subjects**
  - **Clinic visits @ 0, 1, 2, 12, 13, 20 mos.**
    - **AEs since last visit / postcard**
  - **Postcards**
    - **5 times over 1st LD season**
    - **3 times over 2nd LD season (+ 24 mos.)**
- **DSMB**

Solicited Adverse Events (diary card) Efficacy Trial

	Vaccinee (N = 402) %	Placebo (N = 398) %
Redness*	41.8	20.9
Soreness*	4.2	0.0
Swelling*	29.9	11.3
Arthralgia*	25.6	16.3
Fatigue*	40.8	32.9
Rash*	11.7	5.3

*p-value < 0.05

Adverse Events

All Subjects, Reported ≤ 30 d post-vaccination

Efficacy Trial

	Vaccinee (N = 5469) %	Placebo (N = 5467) %
Injection pain*	21.9	6.9
Injection site reaction*	1.5	0.9
Chills/rigors*	2.1	0.7
Fever*	2.5	1.6
Arthralgia	6.8	6.1
Myalgia*	4.8	2.9

*p-value <0.05

Adverse Events

All subjects, > 30 days post-vaccination

Efficacy Trial

	Vaccinee (N = 5469) %	Placebo (N = 5467) %
Arthralgia	13.6	13.6
Arthritis	2.9	2.8
Arthrosis	1.7	1.5
Myalgia	4.0	3.4
Tendonitis	1.9	1.6

No significant differences

History of LD Prior to Vaccination Efficacy Trial

- 1,206 subjects self-reported history LD at entry
  - Increased musculoskeletal AEs, regardless of whether vaccinee or placebo recipient (vs. subjects w/ no history LD)
  - Increased musculoskeletal AEs in vaccinees vs. placebo recipients ≤ 30 d after vaccination
  - No significant difference between vaccinees and placebo recipients w/ history of LD in musculoskeletal AEs >30 d after vaccination

Western Blot Positive at Baseline Efficacy Trial

- **Baseline serology examined in:**
  - **Subjects w/ positive or equivocal Western Blot at a visit for suspected LD**
  - **Subjects found positive on routine testing of all subjects at mo. 12 or mo. 20**
- **Baseline serology: 250+ / 628 subjects tested**
- **Nature & incidence of AEs did not differ between vaccinees Western Blot positive at baseline (n=124) & vaccinees Western Blot negative at baseline (n=151).**

LYMErix® Safety Database

- **18,047 doses of LYMErix® (30ug)**
- **6,478 subjects ≥ 15 years of age**

VRBPAC May 28, 1998

- **Unanimous: pre-licensure data supported safety & efficacy of LYMErix® given @ 0, 1, 12 mo. in adults**
- **Recommended additional post-marketing data**
- **Post-Marketing commitments**
  - **Phase 4 study of 25,000 vaccinees (1vaccinee:3contol)**
  - **Completion of cellular immunity study**
  - **Pre-clinical reproductive toxicity study**
  - **Pregnancy registry**

Post-marketing Commitments LYMErix® December 21, 1998

- **Phase 4 Prospective Cohort Study**
  - **Main purpose: Evaluate LYMErix™ as risk factor for new onset inflammatory arthropathy**
  - **Vaccinees & age-/gender-matched controls (1:3)**
  - **Begun January 1, 1999**
  - **As of November 6, 2000:**
    - **2,568 vaccinees under study**
    - **10% of planned 25,000 Ph 4 vaccinees**

Power to Detect Increases in Adverse Events

- Phase 4 cohort safety study
  - 25,000 vaccinees; 75,000 non-vaccinees
  - 80% power to detect doubling of event occurring in 3/10,000 non-vaccinees

Post-Marketing Commitments
LYMErix® December 21, 1998

Cellular immunity study

Postulated that vaccinees w/ DR4 allele could be at risk for arthritis

- **Lyme arthritis may persist for months/several years despite antibiotic treatment**
- **Association reported between DR4 allele & treatment resistant Lyme arthritis**
- **DR4 is one of several alleles associated w/ disease severity in rheumatoid arthritis**

Post-Marketing Commitments
LYMErix® December 21, 1998

- **Cellular immunity study (cont.)**
  - **Exploratory**
  - **Limited power**
  - **Failed to identify an association between vaccination and arthritis in DR4+ subjects**

THE END